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Cell Shape and Cell Division in Fission Yeast Minireview

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The fission yeast *Schizosaccharomyces pombe* has served as an important model organism for investigating cellular morphogenesis. This unicellular rod-shaped fission yeast grows by tip extension and divides by medial fission. In particular, microtubules appear to define sites of polarized cell growth by delivering cell polarity factors to the cell tips. Microtubules also position the cell nucleus at the cell middle, marking sites of cell division. Here, we review the microtubule-dependent mechanisms that regulate cell shape and cell division in fission yeast.

Introduction

The fission yeast *Schizosaccharomyces pombe* is a unicellular eukaryote that has a cylindrical rod shape of 4 μm diameter and grows by polarized tip extension from 7 to 14 μm in length. Upon reaching 14 μm, cells stop growing and enter mitosis. Cells then divide by assembling an actomyosin contractile ring at the geometrical center of the cell. The subsequent two daughter cells are of equal length — 7 μm. Interestingly, each daughter cell initiates growth immediately from its 'old' tip until the completion of S phase, at which point it also initiates growth at the 'new' tip (i.e. the site of the previous cell division) in a process termed new end take off (NETO) [1]. These seemingly simple acts of growth and division pose two important questions: how does the cell know where to divide, and how does the cell know where to grow? The answers to these two questions appear to involve the dynamic microtubule cytoskeleton.

Antiparallel Microtubule Structures in Fission Yeast

An interphase fission yeast cell has between three and five spatially discrete bundles of microtubules that are dynamic and align with the long axis of the cell (Figure 1A) [2,3]. Our current understanding suggests two complementary models in which interphase microtubule-organizing centers (iMTOCs) contribute to bundle formation. In the first model the iMTOCs are tethered to the nuclear membrane, and in the second model the iMTOCs are dynamically recruited to pre-existing 'template' microtubule lattices. The iMTOCs appear to be tethered to the nuclear membrane by a complex comprising the nuclear envelope proteins Sad1p and Kms2p [4]. Interestingly, the Sad1p–Kms2p complex is embedded in the nuclear membrane to couple the cytoplasmic microtubule cytoskeleton to the nucleoplasmic chromatin [4]. The iMTOCs contain the so-called γ-tubulin ring complexes (γ-TuRCs), which nucleate new microtubules [5]. The γ-TuRCs are themselves recruited to iMTOCs and activated by the Mto1p–Mto2p complex. Upon nucleation, new microtubules are bundled together in an antiparallel configuration at their minus ends by the homodimeric microtubule bundling protein Ase1p [6]. Therefore, in the first model, each microtubule bundle contains the stable minus ends overlapping and connected to the cell nucleus, and dynamic plus ends facing and interacting with the opposite cell tips (Figure 1B) [7,8]. In the second model, newly nucleated microtubules are pulled toward the minus end of the template microtubule by the motor protein Klp2p (Figure 1C) [6]. The new microtubule can then grow and act as a template for nucleation of other microtubules. Electron tomography has revealed that each half of an individual interphase microtubule bundle contains mostly one long primary template microtubule, and several shorter newly created microtubules, consistent with both models [9]. It is not known what restricts the number of iMTOCs to between three and five per cell. Deletion of the Mto1p–Mto2p complex results in cells with one interphase microtubule bundle, but this single bundle is longer and contains more polymers than any of the bundles in wild-type cells [10,11]. Interestingly, loss of the formin For3p, which nucleates actin cables, results in cells with a higher number of microtubule bundles compared with wild type, but these bundles also appear to be shorter than wild type [12]. These results suggest that the equilibrium between tubulin concentration, microtubule nucleators, and regulators of microtubule length may dictate the number and dynamics of interphase microtubule bundles.

The two complementary models described above result in the formation of antiparallel interphase microtubule bundles that contain an inherent symmetrical architecture: stable minus ends are bundled and attached to the nuclear membrane, and dynamic plus ends are facing and interacting with the opposite cell tips (Figure 1). This microtubule architecture is ideal for two biological functions: firstly, microtubules can dynamically position the nucleus at the cell middle, with the nuclear position dictating the future cell division site; and, secondly, microtubules can deliver polarity factors to the cell tips, telling the cell where to grow and thus dictating cell shape.

Microtubule-Pushing Forces Center the Nucleus to Position the Division Site

The position of the interphase nucleus dictates the future site of cell division [13,14]. The so-called medial cortical nodes are protein complexes that localize to the cell cortex at the cell center [15]. These nodes appear to be dynamically tethered to the cell cortex and, as the nucleus moves, the nodes themselves move in response to this nuclear movement [13,16]. In experiments in which the nucleus was centrifuged away from the cell center, the medial nodes also moved away from the cell center [13,16]. In mutant cells with defective microtubule bundles, the nucleus was positioned off-center, resulting in nodes being off-center and therefore leading to a misplaced cell division site and septum. At the start of mitosis, the medial node component Mid1p appears to recruit a series of other proteins to assemble an actomyosin ring for cell division [17]. In this context, nuclear positioning directly regulates cell division site placement. So, what controls nuclear positioning?

As a fission yeast cell grows, its nucleus is dynamically positioned at the geometrical center of the cell. In many organisms, nuclear positioning employs a dynein-dependent

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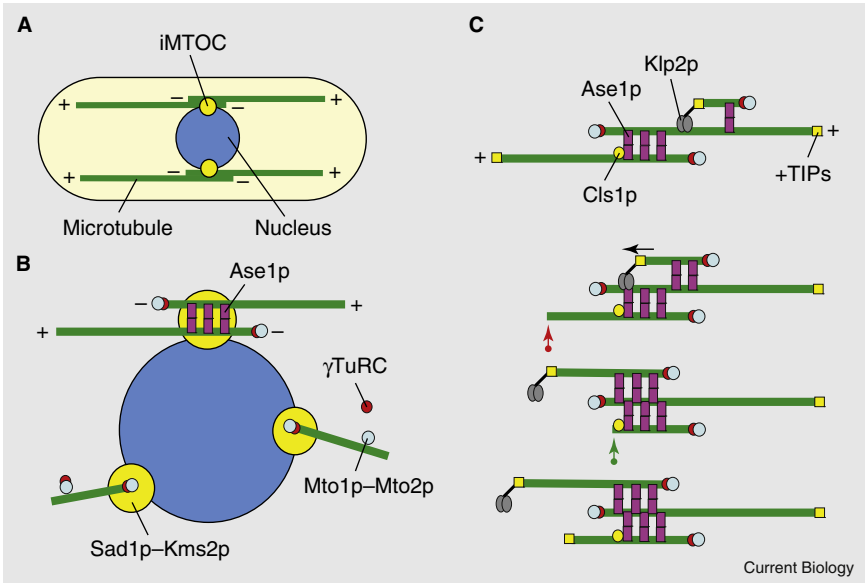

Figure 1. Microtubule organization in fission yeast.

(A) A typical fission yeast cell has between three and five dynamic microtubule bundles organized along the long axis of the cell that are organized by iMTOCs into antiparallel bundles with minus ends overlapping at the middle of the cell and plus ends facing and interacting with the cell tips. Two complementary modes of microtubule organization are presented in (B) and (C). (B) In the first model, iMTOCs are tethered to the nuclear membrane. The Mto1p–Mto2p complex, a component of the iMTOC, recruits γ-TuRCs, which nucleate microtubules. Microtubule polymers are then bundled into an antiparallel configuration by Ase1p. (C) In the second model, new microtubules nucleate on pre-existing microtubules. The Mto1p–Mto2p complex recruits γ-TuRCs to the lattice of a pre-existing microtubule. Ase1p stabilizes the antiparallel configuration between new and old microtubules. The kinesin Klp2p slides the new microtubule to the minus end of the old microtubule (marked by the arrow), establishing an antiparallel bundle. Microtubule length is regulated by +TIP proteins and the rescue factor Cls1p/Peg1p. A growing microtubule can exhibit catastrophe and shrinkage (red arrow). It can then be rescued by Cls1p/Peg1p at the iMTOC and re-grow (green arrow).

microtubule-pulling mechanism [18]. Interphase fission yeast cells instead employ a microtubule-pushing mechanism [3,13,14,19]. Individual microtubule bundles are tethered at their minus ends to the nuclear membrane [4], and their plus ends are dynamically growing and shrinking [2,3]. When a microtubule plus end grows toward the cell tip, it makes transient contact with the cell tip. During this dwell time the microtubule plus end continues to polymerize. As microtubules are structurally stiff polymers [20], this growth translates into a pushing force [21], which moves the nucleus in the opposite direction of microtubule growth [3,13,14,19]. When the microtubule plus end exhibits a catastrophe and begins shrinkage, no pushing force can be exerted on the nucleus. Key parameters that ensure the medial positioning of the nucleus include: the antiparallel architecture of the microtubule bundles; regulation of microtubule dynamics; and cell geometry.

As described above, the interphase fission yeast cell organizes three to five bundles of antiparallel microtubules. This architecture dictates that the number of microtubules opposite each side of the nucleus, and facing opposite cell tips, is always equal. This equality in microtubule number leads to equality in force production when microtubules contact cell tips, and thus ensures that the nucleus is moved to the position of force balance, which is at the geometrical center of the cell (Figure 2). An asymmetry in microtubule number would lead to a misplaced nucleus. The iMTOC protein Rsp1p appears to organize the bundle number, with mutant *rsp1* cells having one large aster-like microtubule bundle instead of the multiple antiparallel bundles seen in wild-type cells [22]. This astral microtubule organization often leads to one side of the cell having more microtubules than the opposite side. The side with more microtubules produces more pushing forces, resulting in the nucleus being pushed off-center [22]. In *mto1* or *mto2* mutants, which have just one microtubule bundle, the nucleus is still correctly positioned at the cell center [23]. However, the variance in the medial position of nucleus in cells with one microtubule bundle is larger than that in wild-type cells with three to five microtubule bundles [23]. Computer simulation has led to similar conclusions, finding that four bundles are better than one bundle in centering the nucleus [3].

Microtubules exhibit dynamic instability, undergoing growth and shrinkage phases, and switching between these two phases with catastrophe and rescue frequencies [2,3]. Wild-type fission yeast microtubules grow persistently from the nuclear region toward the cell tips, with little or no catastrophe until they make contact with the cell tips. The microtubule plus end carries an ensemble of plus-tip-tracking proteins (+TIPs), some of which appear to regulate the lengths of microtubules. The plus-tip proteins Mal3p and Tip1p promote growth and suppress catastrophe [24]. Deletion of *mal3* or *tip1* results in microtubule catastrophe anywhere along the cell cortex, and generally shorter microtubule bundles [24]. The kinesin-8 motor proteins Klp5p and Klp6p also localize to microtubule plus ends [25]. Deletion of *klp5* or *klp6* results in less microtubule catastrophe at cell tips, and overall longer interphase microtubules [26]. *In vitro*, the Klp5p–Klp6p heterodimer can persistently track a depolymerizing microtubule end [27], suggesting that these motors may have microtubule depolymerization activity. No rescue frequency has been reported for fission yeast, probably due to the difficulty of imaging the iMTOC medial region. One report has suggested that the microtubule-binding protein Cls1p/Peg1p localizes to the microtubule plus end and destabilizes microtubules [28], although this finding is controversial. A more recent report has now suggested that Cls1p/Peg1p localizes with Ase1p at the iMTOC region, where it acts as a rescue factor to promote regrowth of a shrinking microtubule [29].

Microtubule-length regulation is important for proper nuclear positioning. As easily imagined, short microtubules not touching the cell tips cannot produce pushing forces to

position the nucleus, and long microtubules curving around the cell tips would not produce efficient pushing forces either. Indeed, *mal3* and *tip1* mutants have nuclear positioning defects [30,31], and *klp5*, *klp6*, and *cls1/peg1* mutants are also expected to have nuclear positioning defects. Interestingly, the physics of microtubule pushing suggest that the pushing force (equivalent to the compressive force experienced by the microtubule as it makes contact with the cell tip) drops off quickly with the increase in microtubule length, approximated by the buckling equation $F = \pi^2 \bullet EI/L^2$, where F is the compressive force, EI is the flexural rigidity of the polymer, and L is the length of the polymer. Although there is currently no *in vivo* value for EI of microtubules, *in vitro* measurements yield an EI value of $\sim 25 \times 10^{-24}$ Nm^2 [20]. This value leads to the estimation that a microtubule that is 1, 10, and 100 μm long can produce pushing forces of 250, 2.5, and 0.025 pN, respectively. For comparison, dynein can generate 7 pN of force [32]. Given that a fission yeast cell is 14 μm long, each half-bundle is expected to have a microtubule of 7 μm in length, producing ~5 pN of force. Large forces have been shown to trigger microtubule catastrophe *in vitro* [21], *in vivo* [25], and *in silico* [33]. Thus, microtubule length regulation will need to be examined in the context of both physical forces triggering catastrophe and the proteins controlling the dynamic parameters of microtubules.

Finally, cell geometry has a profound influence on mechanisms of nuclear positioning. As illustrated above, pushing forces from a single microtubule are productive only when the microtubule is in the order of 10 μm long. The interphase fission yeast has a cylindrical rod shape 14 μm long: this length scale and shape appear to be within the productive pushing force regime. During mating, two haploid yeast cells fuse to form a diploid. The fused diploid nucleus undergoes the so-called horse-tail oscillation, where the nucleus is moved back-and-forth in the cell in a dynein-dependent pulling mechanism [34]. These diploid cells have approximately the same length scale as the haploid cells, yet they use a completely different — and opposite — mechanism of nuclear positioning. The difference between the interphase cell and the diploid cell, which are of similar lengths, is their shape. Diploid cells can be U-shaped, S-shaped, as well as rod-shaped: pushing would appear to be inefficient compared with pulling when either large length scales or complex cell shapes are involved.

It should also be noted that, while the mechanism of microtubule-dependent nuclear positioning described above is one pathway to position the division plane, other mechanisms exist. Recently, the cell tip protein kinase Pom1p has been shown to restrict the position of the kinase Cdr2p, which is a component of the medial nodes and a Mid1p recruitment factor, to the cell center [35,36].

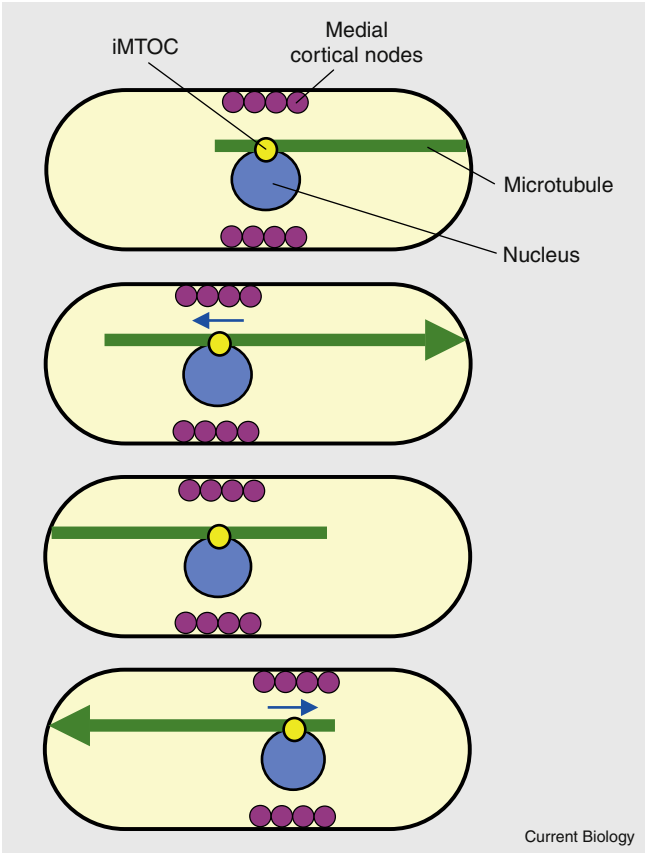

Figure 2. Microtubule pushing centers the nucleus and cortical medial nodes to define the site of cell division.

The iMTOC tethers the microtubule bundle to the nucleus. During microtubule–cortex contact, sustained polymerization at the microtubule plus end produces a pushing force (shown by the large arrowhead) that displaces the nucleus in the opposite direction (nuclear movement depicted by blue arrows). The antiparallel configuration of the microtubule bundle ensures that, over time, the nucleus oscillates back and forth toward the geometrical center of a growing cell. Coupling between the nucleus and the medial cortical nodes ensures that the nodes, over time, are also positioned at the cell middle. The medial nodes subsequently organize the actomyosin ring for cell division.

Microtubules Deliver Polarity Factors to Cell Tips, Dictating Cell Growth and Cell Shape

Our current understanding of fission yeast cell polarity suggests a model in which the actin cytoskeleton directs cell growth and the microtubule cytoskeleton directs where to grow (Figure 3A). In this model, microtubule plus ends contain the so-called +TIP complex [37], which comprises proteins including Tea1p (kelch-repeat protein) and Tea4p (SH3-domain protein) [38,39]. A growing microtubule plus end delivers the Tea1p–Tea4p complex to the tip of the cell, where it docks onto the receptor Mod5p [40]. The Tea1p–Tea4p complex then recruits the polarisome complex, which contains the actin-binding protein Bud6p and the formin For3p [37]. For3p then nucleates actin cables [41,42], which serve as tracks for myosin-based vesicular transport and growth.

We propose a model in which the balance between the rate of delivery ($R_{Delivery}$) of polarity factors to the cell tip and the rate of dispersion ($R_{Dispersion}$) of such factors away from the cell tip dictates the shape of the cell (Figure 3B). It should be noted that each protein involved in the cell shape pathway has both an $R_{Delivery}$ and an $R_{Dispersion}$. In addition, each protein complex named need not be spatially and temporally distinct, as their interactions are complex and may involve local feedback loops [42,43]. This model explains some of the cell shapes observed in various fission yeast mutants (Figure 3C). In wild-type cells, in which the microtubule bundles are spaced equally apart with respect to the long axis of the cell, actin patches and cables are subsequently distributed evenly at the cell tips, leading to a linear direction

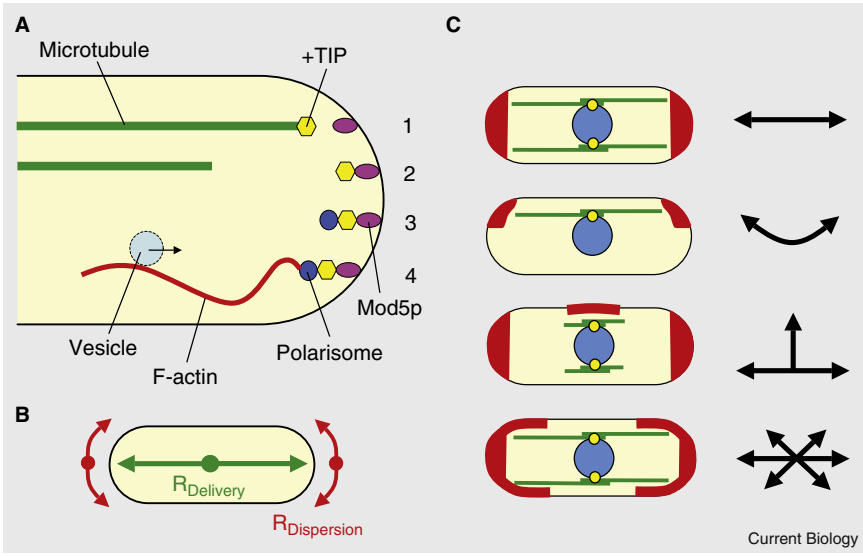

Figure 3. Cell-shape formation in fission yeast.

(A) A scheme of microtubule plus ends delivering polarity factors to the cell tip. The microtubule plus end delivers the +TIP complex carrying the Tea1p–Tea4p complex to the tip of the cell (1), where it is docked on the Mod5p receptor (2). The Tea1p–Tea4p complex recruits the polarisome complex containing Bud6p and For3p (3). For3p nucleates F-actin cables, which serve as tracks for the vesicular transport of the growth machinery to the cell tip (4). (B) A model for how the balance between the rate of delivery ($R_{Delivery}$) and rate of dispersion ($R_{Dispersion}$) of polarity factors defines cell shape. (C) Consequences of changes in the delivery of polarity factors (i.e., $R_{Delivery}$) or changes in the dispersion of polarity factors (i.e., $R_{Dispersion}$) on cell shape. When $R_{Delivery}$ is equal or greater than $R_{Dispersion}$, cells maintain linear growth. When $R_{Delivery}$ and $R_{Dispersion}$ are displaced from the cell long axis, cells grow bent. When $R_{Delivery}$ does not reach the old cell tips, new cell tips are initiated and cells grow T-shaped. Finally, when $R_{Delivery}$ is less than $R_{Dispersion}$, cells grow oval or round.

of growth. In mutant cells with primarily one bundle of microtubules, such as *mto1* and *mto2* mutants, delivery of polarity factors to the cell tip is offset to the site of microtubule contact. This leads to differential growth at the tip of the cell, resulting in a bent direction of growth [10]. In cells with abnormally short microtubules, either following treatment with microtubule-depolymerizing drugs [44], or as exhibited by the +TIP mutants *mal3* and *tip1*, or the tubulin mutant *nda3* [30,31,45], the polarity factors are not delivered directly to the cell tips. Instead, they may be delivered to distances corresponding to the length of the short microtubules. This leads to growth at ectopic sites, resulting in a T-shaped phenotype. In a similar fashion, low and intermediate doses of microtubule-depolymerizing drugs, which resulted in short and intermediate microtubule lengths, also caused ectopic cell tips to grow where the microtubule lengths stopped [44]. Finally, in mutants where cell polarity factors are dispersed, such as the round mutant *orb6*, in which Bud6p is dispersed, growth occurs progressively away from the cell tip, resulting in an oval or round phenotype [46]. Interestingly, deletion of *tea1* or *tea4* resulted in cells making an ectopic cell tip, forming a T shape [38,39], suggesting that the Tea1p–Tea4p complex is not necessary for making ectopic cell tips. In addition, drug-mediated microtubule depolymerization in growing wild-type cells did not produce a T shape [47]; instead, cells maintained linear growth. Taken together, these results suggest that microtubules can initiate sites of polarized growth; however, once initiated, actin can maintain polarized growth independently of microtubules.

This model was also tested directly by targeting microtubules away from cell tips and toward cell sides. Through soft-lithography and microfabrication, two groups independently created microchambers to constrain cells. When straight fission yeast cells are forced into a bent shape by either growing them in curved microchannels [46], or physically forcing them into microwells [46,48], the cells reorganized their microtubules such that microtubule tips could now make contact with the ectopic site on the cell cortex. This microtubule–cortex contact resulted in polarity factors being deposited at the ectopic site [46,48]. In the case where cells were grown in curved microchannels, the ectopic polarity site grew a new cell tip [46]. In contrast, in the case where cells were forced into microwells, and thus abruptly bent, no new tips were observed unless the Tea1p–Tea4p complex was absent [48]. One explanation for the slightly different results is that, by abruptly pushing cells into a microwell, a stress response pathway is activated and thus will delay or inhibit new tip formation [48]. A second explanation may be that, similar to the original findings with *tea1* and *tea4* mutants, new ectopic cell tips can form independently of the Tea1p–Tea4p complex [38,39]. This study highlights multiple redundant pathways leading to new cell tip formation. In addition, when round mutant *orb6* cells, which have a radial microtubule orientation, were forced to grow in straight microchannels, they reorganized their microtubules to the cell long axis, leading to the relocalization of the polarity factors to the cell tips [46]. These results point to a global feedback loop between the microtubule cytoskeleton and cell shape, and a local feedback loop between the actin cytoskeleton and the cell tip.

The story, of course, is not so simple. Recent findings suggest that cell extension is accomplished by a high internal turgor pressure and the cell wall elasticity and is independent of the actin cable nucleator For3p [49]. This work highlights the complexity of the many pathways regulating cell growth and shape. Nevertheless, mathematical models based on modified reaction–diffusion equations are emerging that can recapitulate some aspects of cell-shape formation [50].

Conclusions

In this article, we have outlined simplified models for understanding cell shape and cell division in fission yeast. The microtubule cytoskeleton appears to play key roles in producing the pushing forces for nuclear positioning and division plane placement. The microtubule cytoskeleton is also important in initiating sites of polarized cell growth

and thus determining cell shape. The actin cytoskeleton, however, directs cell growth independently of microtubules. Future work to decipher the many pathways regulating cell shape and cell division promises to be exciting and complex.

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